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EXAMINER

NGUYEN, QUANG

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.A.M.

Office Action Summary**Application No.**

09/764,359

Applicant(s)

REID ET AL.

Examiner

Quang Nguyen, Ph.D.

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) 10, 22 and 37 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 11-21, 23-36 and 38-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-40 are pending in the present application, with claims 1-9, 11-21, 23-36 and 38-40 are examined with the following elected species: (a) liver as a donor tissue; (b) adult as a donor; and (c) hepatic progenitor cell lineage as a species of progenitor cell lineage.

Applicants' amendment filed on 11/26/03 has been entered.

This application contains claims 10, 22 and 37 drawn to an invention nonelected with traverse in Paper No.14. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

Claims 8, 15, 25 are objected to because the claims contain non-elected embodiments or species. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 11-21, 23-36 and 38-40 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons already set forth in the previous Office Action mailed 8/26/03 (page 3)

In claim 1 and its dependent claims, it is unclear what is encompassed by the phrase "non-fetal donor tissue that would be considered unsuitable for an organ transplantation" is unclear. Which conditions or criteria are used for considering a non-fetal donor tissue to be unsuitable or suitable for organ transplantation? These criteria are not explicitly defined in the specification and are inherently subjective. The metes and bounds of the claims are not clearly determined.

Similarly, amended independent claims 16, 21, 23 and their dependent claims, the phrases "obtaining liver tissue from said donor that is not suitable for transplantation", "harvesting the tissue, which is not suitable for transplantation" and "the tissue harvested being suspected of having at least one diploid cell population and not being suitable for transplantation" in claims 16, 21 and 23, respectively, are indefinite for the same reasons stated in the above paragraph.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed 11/26/03 (pages 15-16) have been fully considered, but they are not found persuasive.

Applicants argue basically that the point at which cadaveric liver would be considered unsuitable for organ transplantation is clear to one skilled in the art by directing the examiner to various passages from the specification which describe and define means of determining the unsuitability of cadaveric liver for organ transplantation. For example, "Isolation of liver progenitors from cadaver human liver, as disclosed herein, is novel and unexpected due to the prevailing opinion in the art that liver loses

Art Unit: 1636

its utility due to ischemia" (page 21, lines 30-32); "recent efforts to use such donors have supported the possibility of using them if the liver is obtained within a half hour of death" (page 1, lines 19-20); "no organs are used after heart arrest and, experimentally, none are used after more than one-half hour from the time of heart arrest or asystole" (page 3, lines 4-6), and "The liver can functionally survive for no longer than one hour and transplants from non-heart-beating donors (NHBDs) are recommended to be carried out **preferably** within the first thirty-five minutes of exposure to warm ischemia" (page 3, lines 15-18). Applicants' arguments are respectfully found unpersuasive for the following reasons.

Firstly, claims 1, 6-7 and 11 are not even necessarily directed to obtaining a non-fetal donor tissue that would be considered unsuitable for an organ transplantation from a cadaver.

Secondly, based on the passages "**no organs are used after heart arrest** and, experimentally, none are used after more than one-half hour from the time of heart arrest or asystole" and "**The liver can functionally survive for no longer than one hour** and transplants from non-heart-beating donors (NHBDs) are recommended to be carried out **preferably** within the first thirty-five minutes of exposure to warm ischemia". So, would a liver tissue being exposed to 40 minutes, 50 minutes and 60 minutes of warm ischemia or a liver tissue obtained from a donor after a heart arrest be considered suitable or unsuitable for organ transplantation?

Thirdly, would a liver obtained from a rat be considered to be unsuitable for an organ transplantation in a human or other xenogenic host?

Art Unit: 1636

Accordingly, since the criteria or conditions that are used for considering a non-fetal donor tissue to be unsuitable or suitable for organ transplantation, are not explicitly defined in the specification and are inherently subjective, the metes and bounds of the claims are not clearly determined. Therefore, the claims stand rejected for the reasons set forth above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9, 11-17, 19-20 and 39-40 stand rejected under 35 U.S.C. 102(b) as being anticipated by Reid et al. (WO 95/13697; 1995; IDS) for the same reasons set forth in the previous Office Action mailed 8/26/03 (pages 4-5). Please note that claims 13-15 are amended claims.

With respect to the elected species, Reid et al. disclose methods for isolating hepatoblasts comprising liver stem cells (pluripotent precursors) and committed precursors for either hepatocytes and bile duct cells using panning technologies and

Art Unit: 1636

multiparametric FAC sorting from a single cell suspension of liver cells (see Summary of Invention). Reid et al. state "The methods of the invention have been developed using embryonic and neonatal livers from rats, however, the method of the invention offers a systemic approach to isolating hepatoblasts from any age from any species" (page 4, lines 6-10). This statement includes the isolation of hepatoblasts from adult liver (see page 43). Reid et al. also note that hepatoblasts which are found in a high proportion of liver cells in early embryonic livers and in small number located periportally in adult livers (page 3, line 35 continues to line 1 of page 4). In the disclosed method (page 14, lines 9-15 for example), livers were dissected from donors (the donors should no longer have any heart-beat as a consequence of the removal or from the dissection of the livers), and placed into fresh ice-cold HBSS (should be about 4°C). Additionally, since the livers from the donors are harvested immediately, the liver tissues were obtained within the recited time windows (within about 6 hrs, about 3 hrs, or about 1 h). Reid et al. also teach that the tendency of the isolated cells to aggregate is prevented by maintaining the cells at 4°C and by removing calcium with EGTA (page 39, lines 24-33). The isolated hepatoblast cell populations prepared by the methods taught by Reid et al. are indistinguishable from the composition comprising a population of cells enriched in diploid cells, including progenitors that express alpha-fetoprotein of the presently claimed invention.

Accordingly, the teachings of Reid et al. meet all the limitations of the instant claims, and therefore the claims are anticipated by WO 95/13697.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed 11/26/03 (pages 10-12) have been fully considered, but they are not found persuasive.

Applicants argue basically that Reid does not teach or suggest a method of obtaining progenitor cells from tissue that would be unsuitable for transplantation. Applicants further argue that while the present claims, recite the donor is a non-beating heart donor, the claims also require that the donor organ tissue be unsuitable for transplantation. Applicants also argue that the organ tissue used in the method of Reid was not unsuitable for transplant. While the instant specification teaches that tissue is considered unsuitable for organ transplantation after the tissue has been exposed to a period of ischemia, in particular, warm ischemia. The specification also teaches that organ tissue may be preserved for transplantation by use of preservative techniques, and it is well known in the art that chilling and storing an organ on ice immediately following harvesting the organ from the donor is one prominent means of preserving organ tissue for transplantation.

Applicants' arguments are respectfully found unpersuasive for the following reasons.

Firstly, none of the claims recites that the organ tissue has been exposed to a period of ischemia, in particularly warm ischemia, for a time period such that the organ has suffered irreversible damage and has become "useless", and therefore the organ is unsuitable for organ transplantation.

Secondly, since the criteria or conditions for a tissue to be considered unsuitable for an organ transplantation are not explicitly defined in the specification and are inherently subjective, a dissected liver placed into fresh ice cold HBSS (Ca²⁺-free Hank's balanced salt solution containing 0.04% DNase, 0.8 mM MgCl₂, 20 mM HEPES, pH 7.3) in the method of Reid would be considered to be unsuitable for an organ transplantation, particularly in a human host, for example. Moreover, it is well known in the art that preservation of the viability of cells in an organ or tissue during transplantation is problematic, and that it depends on many factors, including the status of the tissue prior to the removal, the duration of time that the tissue remains outside the body, as well as the procedure utilized to initiate reperfusion of the tissue in the recipient as evidenced by the teachings of Simpkins et al. (U.S. Patent No. 5,824,672; see background section in cols. 1-2). In addition, Simpkins teach that many investigators have explored the effect of adding anti-oxidants (e.g., vitamin E, EPC-K1, 2-mercaptoimidazole derivatives and others) to cells and tissues in isotonic solution prior to implantation into a recipient to reduce adverse effects on transplanted tissues. Thus, a dissected liver placed into fresh ice cold HBSS would hardly be considered to be suitable for any transplantation.

Accordingly, claims 1-9, 11-17, 19-20 and 39-40 stand rejected for the reasons set forth above.

Claims 1-2, 8-9, 11-12, 16-21, 23-26 and 38-40 stand rejected under 35 U.S.C. 102(e) as being anticipated by Faris (U.S. 6,129,911 with the effective filing date

of 7/10/1998) for the same reasons already set forth in the previous Office Action mailed 8/26/03 (page 6).

With respect to the elected species, Faris teach methods for isolating liver cell clusters comprising a liver stem cell and a hepatocyte, and a population of isolated liver stem cells, wherein the stem cells can differentiate into hepatocytes or bile ductal cells (see Summary of the Invention). The isolated liver cell clusters and isolated stem cells are obtained from adult liver tissue from various species such as a mouse, a pig or a human; and that the liver tissue is obtained from deceased donors or cadavers (these donors do not have heart-beats, see col. 5, lines 3-25). Faris teaches that the liver cell clusters are dissociated by enzymatic disruption to destroy the desmosomal junctions, and that the isolated liver stem cells can be further purified using magnetic beads coated with antibodies specific for selective cell markers or FACS sorting (col. 6, lines 54-67).

The methods and compositions taught by Faris meet all the limitation of the instant claims, and therefore U.S. Patent No. 6,129,911 anticipates the instant claims.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed 11/26/03 (pages 12-13) have been fully considered, but they are not found persuasive.

Applicants argue basically that Faris does not teach or suggest obtaining progenitor cells from donor tissues that are considered unsuitable for transplantation. While Faris does disclose that tissue may be obtained from a deceased donor or an

Art Unit: 1636

aborted fetus, the method for isolating progenitors actually disclosed by Faris, at col. 6, lines 5-23, provides that the isolation process begins immediately following anesthetization of the donor, i.e., while the donor is still alive with a beating heart. Therefore, Applicants submit that one skilled in the art would not be taught by Faris that viable progeneitor cells could be obtained from organ tissues that had passed the point of irreparable damage so as to be unsuitable for transplantation as claimed in the present application.

Applicants' arguments are respectfully found unpersuasive for the following reasons.

Firstly, Faris teaches clearly to isolate liver cell clusters and liver stem cells from adult liver tissue from various species such as a mouse, a pig or a human; and that the liver tissue is obtained from **deceased donors or cadavers** (these donors do not have heart-beats, see col. 5, lines 3-25; **particularly lines 7 and 21-22**). The liver tissue which is obtained from deceased donors or cadavers is considered to be unsuitable for transplantation on the basis of the paragraphs found in the present application, which state ""Isolation of liver progenitors from cadaver human liver, as disclosed herein, is novel and unexpected due to the prevailing opinion in the art that liver loses its utility due to ischemia" (page 21, lines 30-32); and "**no organs are used after heart arrest** and, experimentally, none are used after more than one-half hour from the time of heart arrest or asystole" (page 3, lines 4-6).

Secondly, it should be noted that Faris's teachings are not limited to the exemplification in col. 6, lines 5-23.

Accordingly, the methods and compositions taught by Faris meet all the limitation of the instant claims, and therefore U.S. Patent No. 6,129,911 anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21, 23-28, 33-36 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reid et al. (WO 95/13697; 1995; IDS) in view of Faris (U.S. 6,129,911) for the same reasons already set forth in the previous Office Action mailed 8/26/03 (pages 7-9).

Reid et al. disclose methods for isolating hepatoblasts comprising liver stem cells (pluripotent precursors) and committed precursors for either hepatocytes and bile duct cells using panning technologies and multiparametric FAC sorting from a single cell suspension of liver cells (see Summary of Invention, and examples). Reid et al. state “The methods of the invention have been developed using embryonic and neonatal livers from rats, however, the method of the invention offers a systemic approach to isolating hepatoblasts from any age from any species” (page 4, lines 6-10). This statement includes the isolation of hepatoblasts from adult liver (see page 43). Reid et al. also note that hepatoblasts which are found in a high proportion of liver cells in early embryonic livers and in small number located periportally in adult livers (page 3, line 35 continues to line 1 of page 4).

Reid et al. do not teach specifically that the donor has a non-beating heart at a time when the liver tissue is harvested, or that the liver tissue is harvested within about six, three, two or one hour after the heartbeat has ceased.

However, at the effective filing date of the present application Faris already teach that human liver tissue obtained from cadavers (do not have any heartbeats) was used as a source of tissue for the preparation of liver stem cells and liver cluster cells (col. 5, lines 21-23). Faris teaches specifically that it is preferred that the cells are obtained from adult liver tissue rather than the fetal tissue (col. 2, lines 7-10).

Accordingly, at the effective filing date of the present application, it would have been obvious for an ordinary skilled artisan in the art to modify the method taught by Reid et al. by using adult liver tissues obtained from cadavers for the preparation of

Art Unit: 1636

hepatoblasts comprising liver stem cells (pluripotent precursors) and committed precursors for either hepatocytes and bile duct because Faris already teach that human liver tissue obtained from cadavers was used for the isolation of liver stem cells and liver cluster cells.

One of ordinary skilled artisan would have been motivated to carry out the above modification because cadavers provide a large source of liver tissue for the preparation or isolation of liver hepatoblasts or stem cells. Additionally, one of ordinary skilled artisan would have been motivated to obtain liver tissues from fresh cadavers (e.g., within the recited time periods after the heartbeat ceased) to minimize damages to the resident liver hepatoblast or stem cell populations.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed 11/26/03 (pages 13-14) have been fully considered, but they are not found persuasive.

Applicants argue mainly that the present invention is neither taught nor suggested by Reid, either alone or in view of Faris. Applicants further argue that Faris fails to cure the deficiencies of Reid with respect to the use of organ tissue unsuitable for transplantation, specifically the donor has a non-beating heart at the time when the tissue is harvested and that the tissue is harvested within the claimed time windows.

Applicants' arguments are respectfully found unpersuasive because Faris teach clearly that human liver tissue obtained from cadavers (do not have any heartbeats) was used as a source of tissue for the preparation of liver stem cells and liver cluster cells (col. 5, lines 21-23). The liver tissue which is obtained from deceased donors or cadavers is considered to be unsuitable for transplantation on the basis of the paragraphs found in the present application, which state "Isolation of liver progenitors from cadaver human liver, as disclosed herein, is novel and unexpected due to the prevailing opinion in the art that liver loses its utility due to ischemia" (page 21, lines 30-32); and **"no organs are used after heart arrest** and, experimentally, none are used after more than one-half hour from the time of heart arrest or asystole" (page 3, lines 4-6). Additionally, one of ordinary skilled artisan would have been motivated to carry out the above modification because cadavers provide a large source of liver tissue for the preparation or isolation of liver hepatoblasts or stem cells. Furthermore, one of ordinary skilled artisan would have been motivated to obtain liver tissues from fresh cadavers (e.g., within the recited time periods after the heartbeat ceased) to minimize damages to the resident liver hepatoblast or stem cell populations.

Accordingly, claims 21, 23-28, 33-36 and 38-40 stand rejected for the reasons set forth above.

Conclusions

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.


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